

Quality: Moderate (5 points)					
D 2	E 0	O 2	C 1	A 0	B 0

Anthony Wang, Sadie Costello, Myles Cockburn, Xinbo Zhang, Jeff Bronstein, and Beate Ritz. Parkinson's disease risk from ambient exposure to pesticides. *Eur J Epidemiol* (2011) 26:547–555

## Study Overview

This case-control study used geographic information system (GIS)–based model to estimate potential airborne (ambient) contamination from agricultural pesticides among 362 incident cases of Parkinson's disease (PD) and 341 population controls living in the Central Valley of California. Combining data from telephone interviews on demographic and exposure data, using geocoded historical occupational and residential addresses, and estimated ambient pesticides application rates from agricultural uses, the researchers estimated exposure status for all study participants. The study found evidence of a positive association between exposure to paraquat at both self-reported occupational and residential addresses during the period 1974 – 1999 and the risk of PD (OR=1.5, 95 % CI 1.03 to 2.18). However, the risk of PD did not increase for participants exposed to paraquat at workplaces or residences only. At workplaces, combined exposure to ziram, maneb and paraquat was associated with a three-fold increase in the risk of PD. The authors conclude that pesticides affecting different mechanisms that contribute to dopaminergic neuron death may act together to increase the risk of PD.

## Study Details

**Study Participants.** Cases were recruited between January 1998 and January 2007, resided in Fresno, Tulare, or Kern counties, and had lived in California for at least 5 years before diagnosis or interview. Cases were recruited within 3 years of diagnosis, were not in the last stages of a terminal illness, agreed to participate, and were confirmed as having clinically probable or possible PD by a University of California–Los Angeles (UCLA) movement disorder specialist. Of the 563 eligible cases, 84% of them were examined by UCLA specialist. A total of 369 cases were included in the study; of these, 362 provided all information needed for the analyses.

Most of Controls were recruited from randomly selected tax assessor residential units (parcels) in each of the three counties. Authors also mailed letters of invitation to a random selection of residential living units and also attempted to identify head-of-household names and telephone numbers for these parcels using the services of marketing companies and Internet searches. Controls were eligible to participate if they a) did not have PD, b) were at least 35 years of age, c) were currently residing primarily in one of the three counties, and d) had lived in California for at least 5 years before the screening. Only one person per household was allowed to enroll. Of the 755 eligible population controls, 54% declined to participate, were too ill, or moved out of the area before enrollment. A total of 346 controls were enrolled, and 341 provided all information needed for the analyses.

**Exposure Measurement.** Exposure data was collected with telephone interviews. Lifetime residential and occupational addresses were geocoded and ambient pesticide application rates from agricultural uses (in pounds per acre per year) within 500 m of each subject's addresses were estimated by using a validated GIS-based system that combined California Pesticide Use reports (PURs) data and land-use maps. The resulting locations were recorded along with the

relevant year range of residence/work in that location and matched to the appropriate year-specific PUR and land-use data.

By combining the PUR data, land use maps, and geocoded address information, a 500-meter buffers around addresses was created for each year in the 26-year period from 1974 to 1999. Annual ambient exposures to the individual pesticides, maneb, ziram, and paraquat, were calculated for each participant by summing the pounds of pesticides applied in each buffer and weighting the total poundage by the proportion of the acreage treated. For each pesticide, they summed the annual pounds applied per acre to obtain 26 annual exposure values for each pesticide separately for occupational and residential addresses and average pesticide exposures were then calculated for the following exposure time windows: 1974–1999, 1974–1989, and 1990–1999. A participant was considered exposed to a particular pesticide or combination of pesticides when the pounds per acre measured was greater than zero during the time window. Participants who did not work or live in the tri-county area between 1974 and 1999 could not be assigned an exposure estimate and were considered unexposed.

**Outcome Ascertainment.** A diagnosis of clinically probable or possible PD was confirmed by a University of California–Los Angeles (UCLA) movement disorder specialist. The authors do not describe the details of outcome ascertainment, but this reviewer consider that it is very likely that “probable” and “possible” cases of PD were defined as described in Gatto NM et al, 2009.

**Methods of Analysis.** Multivariable unconditional logistic regression methods to calculate odds ratios (ORs) to assess associations between exposure to pesticides and PD. Analyses were stratified by exposure time window, age at diagnosis and area of probable occurrence of exposure (residential area or workplace).

**Confounders Considered.** Estimates were adjusted for age at diagnosis (cases) or age at interview (controls), sex, ethnicity (White vs. non-White), education (<12 years, 12 years, >12 years), having a 1st degree family member with PD (yes, no), and smoking (current, former, never). In some analysis, they also adjusted for organophosphate and organochlorine exposure.

**Effect Measure and Point Estimates.** There was not statistically significant association between ambient exposure to paraquat and PD in the Central California Valley for the 1974–1999 time window of exposure. As compared to those not exposed to paraquat, maneb or ziram, those exposed to paraquat in their self-reported occupational address (81 cases and 78 controls) had adjusted OR=1.26 (95%CI 0.86 to 1.86). Similarly, for those exposed to paraquat in their self-reported residential address (109 cases and 125 controls), the adjusted OR was 0.91 (95%CI 0.63 to 1.31).

As compared to those not exposed to paraquat, those exposed to paraquat in their self-reported occupational address (28 cases and 30 controls) had adjusted OR=1.07 (95%CI 0.59 to 1.96). Similarly, for those exposed to paraquat in their self-reported residential address (71 cases and 90 controls), the adjusted OR was 0.77 (95%CI 0.50 to 1.17).

In contrast, among those exposed to paraquat at both residences and work places (162 cases and 111 controls), it was found a significantly increased in the adjusted odds of PD, OR=1.50 (95%CI 1.03 to 2.18).

As compared to those not exposed to paraquat or maneb, those exposed to paraquat in their self-reported occupational address (118 cases and 102 controls) had adjusted OR=1.37 (95%CI 0.97 to 1.94). Similarly, for those exposed to paraquat in their self-reported residential address (146 cases and 152 controls), the adjusted OR was 0.98 (95%CI 0.70 to 1.38).

As compared to those not exposed to paraquat or ziram, those exposed to paraquat in their self-reported occupational address (107 cases and 99 controls) had adjusted OR=1.30 (95%CI 0.91 to 1.86). Similarly, for those exposed to paraquat in their self-reported residential address (143 cases and 146 controls), the adjusted OR was 0.99 (95%CI 0.70 to 1.41).

### **Strengths and Limitations Discussed in the Paper**

Findings from this study suggest that exposure to paraquat, maneb and ziram may act together to increase the risk of PD more strongly than exposure to each individual pesticide alone or in any combination of two pesticides. While associations between PD and ambient residential exposures to either ziram and paraquat or maneb and paraquat were only significant for the period 1974-1989, similar combinations of ambient exposure at workplace were significantly associated with PD for the periods 1974-1989 and 1990-1999. However, exposure to paraquat alone was not associated with a significant increase of risk of PD. The authors acknowledge that the GIS-based method, which uses a 26-year average pesticide estimate at participants' occupational and residential addresses, cannot be considered a quantitative measure of exposure. Another limitation is that the accuracy of our GIS-based pesticide exposure estimation relies on the quality of self-reported addresses and, for example, occupational address was missing for 26% of cases and controls. They also acknowledge that the imputation of unexposed status to those with missing addresses very likely biased their results.

### **EVALUATION**

Wang A et al. (2011) used a population-based case-control study design to estimate potential airborne (ambient) contamination from agricultural pesticides among 362 incident cases of Parkinson's disease (PD) and 341 population controls living in the Central Valley of California. Combining data from telephone interviews on demographic and exposure data, using geocoded historical occupational and residential addresses, and estimated ambient pesticides application rates from agricultural uses, the researchers estimated exposure status for all study participants. The study found evidence of a positive association between exposure to paraquat at both self-reported occupational and residential addresses during the period 1974 – 1999 and the risk of PD (OR=1.5, 95 % CI 1.03 to 2.18). However, the risk of PD did not increase for participants exposed to paraquat at workplaces or residences only.

A major limitation in the analysis is the definition of unexposed group for studying exposure to paraquat at workplaces or residences only. Members of the reference group should be truly unexposed individuals. If an individual was exposed to pesticides in the residential area or in the workplace area, that person should be considered as exposed, regardless of the suspected place where exposure might have occurred. It would be more appropriate to use a unique truly unexposed group and use it as a reference for comparisons with: 1) the group of individuals exposed only in their residential address, 2) the group of individuals exposed only in their workplace address, and 3) the group of individuals exposed at both, their residential and workplace addresses. Moreover, the ecologic approach used to measure exposure indirectly strongly depends on self-reported past addresses, which may have resulted in misclassification of exposure.

## REFERENCES CITED

Nicole M. Gatto, Myles Cockburn, Jeff Bronstein, Angelika D. Manthripragada, and Beate Ritz. Well-Water Consumption and Parkinson's Disease in Rural California. *Environ Health Perspect* 117:1912–1918 (2009).